May 31, 1995. Applicants have responded to these requests with the above amendment to the title, specification, drawings and abstract. Applicants again point out that they are submitting a Substitute Specification and that the above amendments refer to the page numbers and text of the Substitute Specification.

II. REJECTIONS UNDER 35 USC §112

A. *In vivo* methods

The Examiner objects to the specification and rejects claims 21-26 for lack of enablement for the alleged reason that "the action of growth factors *in vivo* do not correlate with the actions of the same growth factor *in vitro*" (Office Action of June 11, 1996, page 5, second paragraph). The Examiner also states that "The disclosure of the specification fails to address the issues of efficacy, toxicity, or dose/response kinetics, all of which are immensely important if a growth factor is to be used in a method of treatment (Office Action, page 6).

Applicants respectfully traverse this rejection. KGF is member of a family of growth factors which includes acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF) and the related products of the *host* and *int-2* oncogenes. At the time of the invention, the literature reported several examples of growth factors within the FGF family that displayed *in vivo* pharmaceutical wound healing activity. For example, Stenberg *et al.*, *J. Surg. Res.* 50: 47 (1991) reported an enhancement of wound healing by topical treatment of basic

fibroblast growth factor (bFGF) applied to an area contaminated with bacterial overgrowth. Hebda *et al.*, *J. Invest. Dermtol.* 95: 626 (1990) describes the accelerated epidermal wound healing effects when recombinant human bFGF is injected into pigs. A further *in vivo* study of Tsuboi *et al.*, *J. Exp. Med.* 172: 245 (1990) describes the stimulatory wound healing effects when recombinant bFGF is applied locally to healing-impaired mice. (Exhibits 1-3, respectively). This art, which is contemporaneous with the present invention, clearly supports the enablement of applicants' claimed invention.

Moreover, more recent work has demonstrated the *in vivo* use of KGF in numerous animal models for a variety of purposes. For instance, the effects of KGF in epidermal wound healing using a porcine model was described in Staiano-Coico, *et al.*, *J. of Exp. Med.* 178: 865-878 (1993) (Exhibit 4); the effects of KGF in stimulating skin cells to proliferate and differentiate in rabbit models was reported in Pierce *et al.*, *J. of Exp. Med.*, 179: 831-840 (1994) (Exhibit 5); the effects of KGF in stimulating the proliferation of epithelial cells in the intestinal system was disclosed in Thomason, A., "Peptide Growth Factors in the GI Tract," *Abstract of American Gastroenterology Association Meeting* (June 1994) (Exhibit 6); and, the effects of KGF in repairing lung tissue in rats was disclosed in Panos, R., "Keratinocyte Growth Factor (KGF) prevents hyperoxia-induced mortality in rats," *Abstract, ATS International Conference* (May, 1995) (Exhibit 7). Several other recent papers indicate that KGF has profound and potentially beneficial effects *in vivo*. For instance, Ulich *et al.*, *J. Clin. Invest.* 93: 1298 (1994) (Exhibit 8)

showed that KGF rapidly and specifically induces proliferation and differentiation of Type II pneumocytes in the normal adult lung. Housley, *et al.*, *J. Clin. Invest.* 94: 001-0014 (1994) (Exhibit 9) demonstrated that KGF induces the proliferation of hepatocytes and epithelial cells throughout the rat gastrointestinal tract. Ulich, T., *et al.*, *Am. J. Pathol.* 144: 862 (1994) (Exhibit 10) demonstrate that KGF injected intravenously caused dramatic proliferation of mammary epithelium in mammary glands of rats so as to cause ductal neogenesis and intraductal epithelial hyperplasia. Alarid, *et al.*, *PNAS (USA)* 91: 1074-1078 (1994) (Exhibit 11) disclose that the addition of KGF neutralizing antibody to developing seminal vesicles in whole organ cultures caused a striking inhibition of seminal vesicle growth and morphogenesis. Lacey *et al.*, *ASH Abstract*, 38th Annual Meeting, Orlando, Fla. (December 6-10, 1996) (Exhibit 12), disclose that KGF promotes survival of mice transplanted with syngeneic bone marrow or G-CSF mobilized peripheral stem cells following lethal radiation. Lacey *et al.*, *ASH Abstract*, 38th Annual Meeting, Orlando, Fla. (December 6-10, 1996) (Exhibit 13), disclose that KGF protects mice from chemotherapy and radiation induced gastro-intestinal injury and mortality.

With regard to claim 27, applicants again direct the Examiner's attention to Alarid (Exhibit 11), which describes the use of KGF-neutralizing monoclonal antibody to inhibit seminal vesical growth and morphogenesis in organ cultures. Although Alarid doesn't disclose an *in vivo* study, the presented results are nevertheless suggestive of an *in vivo* use of antibodies against KGF to prevent cell growth. Organ culture systems have been shown to be faithful models of processes that occur *in*

vivo. Riethmüller *et al.*, Monoclonal antibodies in cancer therapy," *Current Opinions in Immunology* 5: 732-739 (1993) (Exhibit 14) is an article reviewing the use of monoclonal antibodies in cancer therapies. The authors opine that monoclonal antibodies may be useful in the treatment of certain cancers, particularly when disease is not extensive. Wherry *et al.*, "Tumor necrosis factor and the therapeutic potential of anti-tumor necrosis factor antibodies," *Critical Care Medicine*, 21(10): S436-S440 (1993) (Exhibit 15) and Bodmer *et al.*, "Preclinical review of anti-tumor necrosis factor monoclonal antibodies," *Critical Care Medicine* 21(10): S441 (1993) (Exhibit 16) both summarize the results of animal studies in which monoclonal antibodies to tumor necrosis factor were found to be beneficial in treating septic shock. Lee *et al.*, "Monoclonal antibodies specific for rat relaxin," *Endocrinology* 130: 2386 (1992) (Exhibit 17) and Nishikawa *et al.*, "In utero manipulation of coat color formation by a monoclonal anti-c-kit antibody", *EMBO* 10(8): 2111 (1991) (Exhibit 18) describe *in vivo* animal studies with specific monoclonal antibodies directed against either a ligand (relaxin) or a receptor (c-kit). In both studies, the goal was to interrupt a normal process rather than to attenuate a pathological process.

In view of this large body of work reporting the *in vivo* use of KGF for stimulating epithelial cell growth and supporting the *in vivo* use of antibodies to prevent biological processes, applicants respectfully request the examiner to reevaluate and reverse her position with regard to the lack of enablement of the claimed invention.

B. Scope of claims

The Examiner rejects claims 21, 22, 26 and 28 and claims dependent thereon for lack of enablement, arguing that "[t]here is no evidence of record regarding the upper limit of specific activity for KGF" (Office Action, page 10, lines 14-15). The Examiner also objects to the term "unique portion" in claim 27; the term "comprising" in claims 24 and 27; and, the term "functional domain" in claim 25.

In response, applicants assert that these objections have been overcome with the above amendments. With regard to the Examiner's objection to the term "comprising," applicants argue that the determination of whether a given polypeptide would have "preferential mitogenic activity on cells of epithelial origin" would be a matter of routine experimentation in view of applicants' own teachings of BALB/MK assays. Accordingly, applicants respectfully request the Examiner to reconsider and withdraw this rejection.

C. §112, second paragraph

The Examiner rejects claims 21-28 and dependent claim 29 under 35 U.S.C. §112, second paragraph, as being indefinite on account of the recitation "a specific activity of at least about". The Examiner also rejects claims 23, 24 and 27 on account of an alleged confusion due to the numbering of amino acids; objects to "functional domains" and "different member" in claim 25; objects to "unique portion" in claim 27; and requires an indication of "what is being stimulated or inhibited" in claims 21-29. In response, applicants assert that all of

these objections have been overcome with the above amendments.

CONCLUSION

In view of the above amendments, arguments and documentary support, applicants assert that claims 21 and 23-37 meet all requirements under 35 U.S.C. § 112 and, therefore, are in condition for allowance. Early notification thereof is respectfully requested.

Respectfully submitted,

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The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741.